UNITED STATES DISTRICT COURT
NORTHERN DISTRICT OF OHIO
EASTERN DIVISION

IN RE: NATIONAL PRESCRIPTION OPIATE LITIGATION	MDL No. 2804
THIS DOCUMENT RELATES TO:	Case No. 1:17-md-2804
Track Three Cases	Judge Dan Aaron Polster

REPLY IN SUPPORT OF DEFENDANTS' MOTION TO EXCLUDE CERTAIN OPINIONS AND TESTIMONY OF DR. KATHERINE KEYES

TABLE OF CONTENTS

Page

TABLE OF AUTHORITIES

Page(s)

CASES

OTHER AUTHORITIES

RULES

INTRODUCTION

Defendants' arguments are straightforward and correct, not a "shell game" as Plaintiffs colorfully put it (before omitting key points, and either omitting or mischaracterizing arguments that Defendants made in their Memorandum).

First, contrary to Plaintiffs' assertions, Opp'n 2–10, and as discussed in Defendants' Memorandum (ECF No. 3858-2 at 4–11) and below, the Court should exclude Dr. Keyes' marketing opinions in Track Three, just as they were in Tracks One and Two. Plaintiffs argue that the record here is different than Track One, where this Court excluded Dr. Keyes' marketing opinions. Opp'n 4–6. That may be so, but Plaintiffs imply ignore the fact that Judge Faber had the *same* record and arguments before him when he excluded those same opinions in Track Two. Moreover, Dr. Keyes' qualifications have not changed, and the record does not differ in any material way from Track One. Setting aside her lack of qualifications to offer marketing opinions, the Court should bar Dr. Keyes from offering such opinions because: (1) her methodology is unreliable as to Defendants; (2) her opinions do not "fit" this case; and (3) allowing her to offer her marketing opinions would be misleading, confusing, and unfairly prejudicial. With their Opposition, Plaintiffs' drive home these arguments. In hopes of salvaging Dr. Keyes' marketing opinions, Plaintiffs attempt to recast those opinions, which, if valid at all, relate to a specific type of marketing (i.e., direct marketing to prescribers) by specific entities (i.e., manufacturers) into opinions about "marketing generally." *See, e.g.*, Opp'n 7. This argument underscores the lack of a valid methodology, fit, and Plaintiffs' intention to violate Federal Rule of Evidence 403. Dr. Keyes' marketing opinions are not the stuff of proper expert testimony, and the Court should preclude her from offering them at trial.

Second—although they do not dispute that Dr. Keyes (i) has never published her opinions about synthetic opioid-related harms, (ii) cites no studies to support them (which is inconsistent

with her literature review methodology), and (iii) has not tested her opinions in any way—Plaintiffs say the Court should go ahead and admit them anyway. Opp'n 10–17. They are wrong, and their arguments to the contrary lack merit. In seeking to exclude Dr. Keyes' unsupported opinions regarding synthetic opioid-related harms, Defendants are not attempting to revisit this Court's decision that Dr. Keyes can testify about the relationship between heroin and prescription opioids, an opinion for which Dr. Keyes cited studies.[1] *See, e.g.*, ECF No. 3858-2 at 12–16; *see also, e.g.*, ECF No. 3858-4 at 39 (citing no studies the "estimate that approximately 70–80% of fentanyl-involved opioid deaths are attributable to prescription opioid use"). As Plaintiffs acknowledge, these opinions regarding synthetic opioid-related harms are based on "inference[s]," Opp'n 17, and Defendants' Memorandum and this Reply explain why "inferences" that prescription opioids are "responsible" for harms caused by the relatively recent introduction of illicit synthetic opioids into the illicit drug supply are flawed and amount to Dr. Keyes' untested say-so. Plaintiffs have no effective answer to this.

Third, while acknowledging that Dr. Keyes is not testifying to legal causation, when she uses the term causation or words meant to convey causation (e.g., attributable), Plaintiffs argue that such testimony is proper and does not require any limiting instruction. Opp'n 18–19. Plaintiffs are incorrect for the reasons discussed in Defendants' Memorandum. ECF No. 3858-2 at 16–18, and below. At a minimum, the Opposition demonstrates exactly why a limiting instruction is necessary. Out of the side of their mouths, Plaintiffs say that Dr. Keyes will not discuss legal causation, Opp'n 18. At the same time, out of the other side of their mouths, Plaintiffs assert that she will be discussing "factual causation," *id.*, and that her testimony should not be precluded

[1] Defendants have preserved their objection to this Court's earlier ruling regarding Dr. Keyes' "gateway" hypothesis on the relationship between heroin and prescription opioids. *See* ECF No. 3858-2 at 2 n.2 & ECF No. 3797.

"merely because she may use particular words *attributing a causal relationship*," *id.* at 19 (emphasis added). No jury—and perhaps not even a lawyer steeped in this case—will understand the lines Plaintiffs are attempting to draw (*i.e.*, Dr. Keyes' use of the word "causal relationship" means something different than "legal causation"), and a limiting instruction to distinguish between an expert's use of "words *attributing a causal relationship*" and legal causation is required. That means such testimony flunks the most fundamental requirement for expert opinion: that "the expert's scientific, technical, or other specialized knowledge will help the trier of fact to understand the evidence or to determine a fact in issue." Fed. R. Evid. 702(a).

ARGUMENT

I. THE COURT SHOULD EXCLUDE DR. KEYES' MARKETING OPINIONS.

The Court should exclude Dr. Keyes' marketing opinions for several reasons, including because two separate courts, in Tracks One and Two, determined that she lacks the qualifications to offer them. ECF No. 3858-2 at 6. As an initial matter, the Court should reject outright Plaintiffs' argument (*see, e.g.*, Opp'n 1 & 7) that Dr. Keyes should be allowed to offer opinions about "marketing generally." Her report contains no such opinion. On the contrary, she only offers an opinion that direct marketing by manufacturers to physicians increased opioid prescribing. *See* ECF No. 3858-4 at 14 ("The increase in opioid prescribing was driven by a multitude of factors, including *direct marketing to physicians . . . .*") (emphasis added); *id.* at 33 (The supply of opioids was also facilitated by pharmaceutical *promotional activity to physicians.* While I did not evaluate *the specific marketing materials of the manufacturers . . . .*") (emphasis added). To support those opinions, Dr. Keyes cites studies that relate solely to marketing by manufacturers to physicians, not "marketing generally." *See* ECF No. 3858 at 7–10; *see also* ECF Nos. 3858-13–3858-23; ECF No. 3858-8 at 105:24–106:8 ("I am not offering opinions about specific marketing activities of specific pharmacies or pharmacy chains. I am offering opinions about these articles in generality,

in aggregate."). Beyond that, Plaintiffs do not dispute—nor could they—that, as discussed in Defendants' Memorandum and testified to under oath by Dr. Keyes herself, those studies relate to marketing by manufacturers—not "marketing generally"—and not marketing by any pharmacy, much less any Defendant. *See* ECF No. 3858-2 at 7–10. Having disclosed no opinions related to "marketing generally," having cited no studies related to "marketing generally," having reviewed no evidence produced by any Defendant at all, and having spoken to not a single prescriber in Lake County or Trumbull County, Dr. Keyes should not be allowed to offer opinions on "marketing generally."[2] *See, e.g.*, *Mathis v. Roa*, 793 F. Appx. 367, 370 (6th Cir. 2019) ("[A]n expert who will testify at trial must submit an expert report setting forth the opinions he is offering and the bases for those opinions. Fed. R. Civ. P. 26(a)(2)(B). Expert testimony at trial that exceeds the scope of that report or sets forth a new theory of the case is subject to exclusion under Rule 37."). Moreover, testimony regarding marketing to physicians by manufacturers, while perhaps relevant to show alternative causes for the alleged opioid crisis, cannot be a basis for assigning public nuisance liability to pharmacies. Indeed, Plaintiffs' Opposition is revelatory—and confirmatory[3]—about how allowing Dr. Keyes to offer her marketing opinions in this case, as Plaintiffs incorrectly frame them, would be confusing and misleading to the jury and, ultimately, unfairly prejudicial to Defendants.

[2] In fact, when Dr. Keyes was asked at her deposition to provide information on "everything you know about marketing to [sic] pharmacies," she responded: "Everything I know about – if there's a specific document that you would like me to review, I can –I can do that. Otherwise, I would prefer to stick to what is in my report." ECF No. 3858 at 83:11–18.

[3] *See* ECF No. 3858-2 at 11 (discussing danger of Dr. Keyes' marketing opinions misleading and confusing the jury, and unfairly prejudicing Defendants).

A. Dr. Keyes' Qualifications Have Not Changed Since This Court and Judge Faber Excluded Her Marketing Opinions in Tracks One and Two, and this Court Should Reach the Same Result in Track Three.

Although Plaintiffs spend a lot of time arguing that the record on Dr. Keyes' qualifications differs from Track One (an argument addressed below), they fail to acknowledge that, in Track Two, the record was substantively the same as it is here,[4] and Judge Faber nevertheless excluded Dr. Keyes' marketing opinions from a bench trial. *See* ECF No. 3858-11. While Plaintiffs suggest that Judge Farber's opinion is not persuasive (Opp'n 6 n.6), the better reading of that opinion is the correct one: Dr. Keyes' qualifications have not changed, and she remains unqualified to offer her marketing opinions.

Plaintiffs are incorrect that the record is meaningfully different here than in Track One regarding Dr. Keyes' qualifications. Her qualifications have not changed, and Plaintiffs do not argue that they have. Instead, they argue that this Court lacked certain information when it previously excluded Dr. Keyes' marketing opinions. Opp'n 4–6. First, they argue that Dr. Keyes is an investigator in a study that involves detailing (*i.e.*, face-to-face meetings with doctors by manufacturers' sales representatives). *Id.* at 4. That may be so, but Dr. Keyes never mentioned that study as supporting her opinions in this case, and she admits she did not meet with a single doctor in Lake and Trumbull Counties. *See* ECF No. 3858-2 at 4–7; ECF No. 3858-8 at 91:19–92:13. More to the point, that study cannot have anything to do with the *Pharmacy Defendants'* liability in this case, except perhaps to show alternative causation. Second, Plaintiffs state that Dr. Keyes

[4] *See* Opp'n 4–6; *Compare* ECF No. 3858-4 at 2 & 33–34 *with* Reply, Ex. 1 at 4 & ECF No. 3868-6 at 29–30. *See also City of Huntington v. AmerisourceBergen Drug Corp.*, No. 3:17-01362 (S.D.W. Va.) (Oct. 20, 2020), ECF No. 1112 at 1 (arguing the "factual record in this case is significantly different from the record before Judge Polster"), *id.* at 5 (discussing Dr. Keyes role as an investigator in a study analyzing detailing), *id.* at 10 n.9 (citing the same study Plaintiffs cite in footnote 3 of their Opposition). The sole difference is that Dr. Keyes added a section where she discusses the Bradford Hill factors. As discussed in footnote 6, that is not a change in Dr. Keyes' qualifications. Nor is it a change to the record. Even in cases where Dr. Keyes' report did not discuss the Bradford Hill factors, Dr. Keyes maintained that she considered them. *See, e.g.*, Reply, Ex. 2 at 55–58, 114–16.

has written twenty-eight peer-reviewed articles related to opioids. Opp'n 4. Again, however, Dr. Keyes did not cite a single one of those articles in support of her marketing opinions. *See* ECF No. 3858-4 at 14 & 33. The one study that Plaintiffs discuss in a footnote, Opp'n 6 n.6, did not evaluate an association, let alone a cause-and-effect, relationship between marketing and prescribing.[5] Lastly, Plaintiffs argue that Dr. Keyes added four new studies to the ones she previously listed. Opp'n 5. That should not alter this Court's analysis from Track One, however. None of those studies relates to a relationship between marketing of prescription opioids to prescribers and the prescribing of prescription opioids. *See* ECF No. 3858-2 at 7 n.9.[6]

Dr. Keyes has been found unqualified to offer her marketing opinions in Tracks One and Two. Plaintiffs have offered no convincing reason why the ruling should be any different now. And indeed, such a ruling would encourage the Parties to do precisely what the Court has discouraged Parties from doing up until now: repeatedly addressing issues that have already been decided.[7]

[5] The study, which was written in 2013 before Dr. Keyes' Track One report was filed, is described by the authors as "aimed to analyze the epidemiology of prescription opioid-related overdose deaths in New York City (NYC) in the period leading to emergence of the epidemic (1990–2006) by examining longitudinal trends and geographic differences within this city." Opp'n, Ex. 1 at 3.

[6] Plaintiffs also argue that Dr. Keyes' "so-called "exhaustive analysis" of the Bradford Hill factors, which constitutes a paragraph of conclusory statements, somehow relates to her qualifications. Opp'n 5–6. To the extent relevant, such considerations go to methodology, not qualifications. Moreover, while Dr. Keyes states that the "results of the studies, are consistent with many of Hill's causal criteria . . .", ECF No. 3858-4 at 33, she fails to note what the three studies related to marketing of prescription opioids (all with the same lead author, Scott Hadland) actually state about causation. The Hadland study that she discussed notes that reverse causation could not be ruled out. ECF No. 3858-19 ("[O]ur findings demonstrate associations between opioid marketing and subsequent prescribing and mortality from overdoes; we cannot exclude reverse causation."); s*ee also* ECF No. 3858-16 ("Limitations include the possibility of reverse causality because physicians who receive industry payments may be predisposed to prescribe opioids. Our findings establish an association, not cause and effect."); ECF No. 3858-18 (study examined payments, but did not look at relationship between payments and prescribing).

[7] *See, e.g.*, ECF No. 3735 at 3 (directing the parties to meet and confer "on mechanisms to avoid . . . duplicative briefing while preserving the record based on motions filed in separate tracks of the MDL"); *see also* ECF No. 3769 (same language in Track Seven Case Management Order).

B. Dr. Keyes' Methodology is Unreliable as to Defendants. Plaintiffs Do Not Dispute that She Never Reviewed Any Evidence or Studies that Concern Marketing by Defendants, as Opposed to Manufacturers' Direct Marketing.

In arguing that Dr. Keyes' methodology is reliable, Plaintiffs ignore the bulk of Defendants' argument. *Compare* Opp'n 6–7 (focusing on Defendants' argument that Dr. Keyes did not consider *any* evidence provided by Defendants or specific to the relevant jurisdictions) *with* ECF No. 3858-2 at 7–10. Specifically, Plaintiffs fail to address that the articles Dr. Keyes reviewed and relies on do not relate to "marketing generally," as Plaintiffs now assert, or to Defendants at all. *Id.* As Dr. Keyes previously testified under oath and the articles show, they relate to direct marketing by manufacturers. ECF No. 3858-9 at 149:10–15; ECF No. 3858-8 at 91:2–5; *see also* ECF No. 3858-2 at 6–10. Dr. Keyes' report also concedes that the studies she reviewed were limited to this type of marketing:

> [I]t is important to note that payments to physicians are only one type of promotional activity, and accounted for only a proportion of the overall promotion strategy for opioid pharmaceuticals. These specific studies do not preclude potential effects of other kinds of marketing efforts; they do, however, provide empirical evidence for the marketing efforts for which data are available to academic researchers. These results confirm through independent epidemiological analysis that *outreach and payments to physicians through the pharmaceutical companies* was an important way in which the distribution of opioids across the United States was facilitated.

ECF No. 3858-4 at 33–34 (emphasis added).

It would be methodologically unsound (and a violation of Federal Rules of Evidence 403 and 702) for Dr. Keyes to review articles about specific marketing by manufacturers to prescribers and then to opine that they speak to "marketing generally"[8] and relate to the activities of the

[8] It bears repeating that the articles do not find causation; they often do not relate to marketing of prescription opioids at all; and that they relate to specific types of marketing. ECF No. 3858-2 at 6–10; ECF Nos. 3858-13–3858-23.

Defendants.[9] Yet, at her deposition, that is exactly what Dr. Keyes previewed she intended to do (ECF No. 3858-2 at 8–11), and what the Plaintiffs confirm they intend to do in their Opposition, *see, e.g.*, Opp'n 7 ("Dr. Keyes summarizes the consistent evidence that marketing *in general* increases the supply of prescription opioids and that the increase in the supply of prescription opioids here was caused, in part, by marketing *generally*.") (emphasis in original). This Court should reject Dr. Keyes' opinions because they lack any methodology that would allow Dr. Keyes to opine on marketing generally.[10]

C. Dr. Keyes' Marketing Opinions Do Not "Fit" This Case, Because They Will Not Help the Trier of Fact. Indeed, Plaintiffs' Description of Dr. Keyes' Opinions and Other Statements Confirm that Allowing Dr. Keyes to Opine on Marketing Would Be Misleading, Confusing, and Unfairly Prejudicial.

Dr. Keyes marketing opinions do not "fit" this case, because they will not "help the trier of fact." Fed. R. Evid. 702(a). If anything, they will violate Federal Rules of Evidence 403 and 702 by misleading and confusing the jury.

In their Memorandum, Defendants expressed concern that Plaintiffs would misleadingly suggest that Defendants engaged in direct marketing to doctors. ECF No. 3858-2 at 11. In making that argument, Defendants believed that Plaintiffs at least would show fidelity to Dr. Keyes' opinions, as disclosed in her report and as discussed in other cases, as well as the subject matter of the studies on which she relied. Defendants were wrong. Plaintiffs' intentions are even more improper than feared. Rather than present Dr. Keyes' marketing opinions and the studies on which

[9] Plaintiffs do not dispute that Dr. Keyes does not have any opinions specific to the Defendants, that she did not review any evidence or testimony provided by them in any case, that she did not speak to any prescribers in Lake County or Trumbull County, and that she previously testified under oath that the studies do not point to the Defendants. ECF No. 3858-2 at 6–10; *see also* ECF No. 3858-9 at 149:10–15.

[10] Plaintiffs also suggest that Dr. Keyes will provide "background" testimony on marketing, Opp'n 1, but she has no background in marketing, ECF No. 1868-2 at 5. The only "background" information that she might provide is, as she admits, what can be gleaned from the studies that she reviewed—specifically, that manufacturers engaged in direct marketing. *See, e.g.*, ECF No. 3858-8 at 87:20–91:16.

she bases those opinions honestly—namely, that they relate to how direct marketing by manufacturers to prescribers increased prescribing—Plaintiffs have left no doubt that they intend to offer misleading and confusing testimony "that marketing *in general* increases the supply of prescription opioids and that the increase in supply of prescription opioids here was caused, in part, by marketing *generally*." Opp'n 7 (emphasis in original). Indeed, they assert that: "It makes no difference, for purposes of Dr. Keyes' epidemiological analysis, *who* was doing the marketing that caused the increase." *Id.* (emphasis in original).[11] Of course it does. Dr. Keyes' opinions would be relevant to Defendants *only* if she connected that marketing activity in question (general, specific, or otherwise) to the Defendants. She does no such thing. It would be misleading and confusing to the jury, and unfairly prejudicial to Defendants, if Dr. Keyes were allowed to transform her analysis of studies about direct marketing by *manufacturers* and increased prescribing—studies Dr. Keyes admits have nothing to do with the chain pharmacies—into opinions about "marketing generally" on "supply" generally. This Court should not allow it.

Given that Dr. Keyes' opinions relate to manufacturers, and that she has not evaluated any Defendant's conduct, or whether any Defendant's conduct affected prescriber behavior, Plaintiffs cannot argue that her marketing opinions will directly "assist the trier of fact" to determine whether any Defendant caused a public nuisance.[12] Instead, Plaintiffs advance the following argument:

[11] The "it makes no difference" argument is just part and parcel of the misleading, confusing, and unfairly prejudicial way Plaintiffs intend to present their case. Rather than focus on specific conduct, Plaintiffs make clear that they want to use improper terms that they have coined for this litigation, such as "pharmaceutical opioid industry," Opp'n 8, to attempt to lump various entities together. Such tactics should not be allowed, even as to the Defendants in this case, which are separate entities, and against whom Plaintiffs have to offer individual proof.

[12] Again, her marketing opinions, if honestly presented, might be relevant to alternative causation (i.e., whether manufacturers' marketing led licensed prescribers to write additional prescriptions for opioid medications), but Dr. Keyes' opinions are not relevant as to Defendants.

> Dr. Keyes testimony, when viewed alongside documents presented through other witnesses that show the Pharmacies were aware that the manufacturers were engaged in aggressive marketing techniques and marketed opioids aggressively themselves, will help the jury determine that the Pharmacies were on notice of the need to create effective controls against diversion, which they then manifestly failed to do.

Opp'n 9. That argument is disingenuous.

First, to the extent the law requires "effective controls against diversion," Defendants do not intend to argue that they did not need to comply with the Controlled Substances Act. The Court will instruct on the law.

Second, Dr. Keyes' marketing opinions have nothing to do with notice. She offered those opinions for the first time in this litigation, and no evidence exists that Defendants were aware of the studies she cites. The studies also do not suggest that prescriptions were written by prescribers for reasons other than what the prescriber viewed as a legitimate medical purpose. ECF Nos. 3858-13–3858-23.

At bottom, what Plaintiffs are really trying to do is illegitimately attribute marketing by manufacturers to the Pharmacy Defendants.[13] Plaintiffs cite a 2020 Purdue plea agreement for the proposition that "Pharmacies were aware that the manufacturers were engaged in aggressive marketing." Opp'n 9 & n.12. Putting aside that Plaintiffs are using a third party's plea agreement for an improper purpose that would violate, among other things, the Federal Rules of Evidence on hearsay, Plaintiffs' characterization of what the document shows is incorrect. Among other things, the Purdue plea agreement is from 2020; it discusses Purdue, not manufacturers generally; and, if

[13] It is for this reason that Plaintiffs' cross-reference to their Opposition to Defendants' Motion to Exclude Anna Lembke is meaningless. Dr. Lembke's report contains no discussion of Defendants marketing to prescribers. Dr. Lembke's opinions should also be excluded. *See* Mot. to Exclude Anna Lembke & Reply in Supp. of Mot. to Exclude Anna Lembke.

anything, it shows that Purdue adjusted its marketing strategies, in part, because pharmacists were vigilant regarding its medications. *See, e.g.*, Opp'n, Ex. 2 Addendum A ¶¶ 7 & 205.

Plaintiffs' solution to the unfairly prejudicial, confusing, and misleading opinion they want to offer is that, "to the extent the Pharmacies wish to highlight that Dr. Keyes does not offer any opinions on their specific marketing, they will have ample opportunity to do so on cross-examination." Opp'n 10. That is no solution, especially in this case with its time limits. Defendants should not need to spend precious time correcting testimony that can only mislead and confuse the jury. Worse yet, in response to Defendants' request that, if Dr. Keyes' opinion is allowed at all, there should be a limiting instruction, Plaintiffs claim that "a limiting instruction would run the risk of creating a false impression to the jury that the Court believes that the Pharmacies did not engage in marketing."[14] *Id.* That is incorrect. A limiting instruction would carefully, and appropriately, delineate the correct boundaries of Dr. Keyes' opinion (i.e., that Dr. Keyes' marketing opinions and the studies that she reviewed relate to marketing by manufacturers to prescribers), avoiding the misleading, confusing, and unfairly prejudicial result that Plaintiffs seek.

In sum, Dr. Keyes' opinions will not "assist the trier of fact" in this case; instead, they will mislead and confuse the jury, resulting in unfair prejudice to Defendants.

[14] This argument makes no sense. First, it confirms that Plaintiffs want to invite the improper inference that Dr. Keyes would be testifying about alleged marketing by Defendants, instead of the direct marketing by manufacturers that she (and the studies on which she relies) discuss. Second, the limiting instruction would not say that Defendants did not engage in marketing or preclude Plaintiffs from offering such proof, to the extent it exists. Instead, a limiting instruction would state something along the following lines: Dr. Keyes offered opinions on marketing. The studies that she reviewed relate to direct marketing by manufacturers; therefore, her marketing opinions are limited to an assessment that direct marketing to prescribers by manufacturers led to increased prescribing by licensed prescribers.

II. THE COURT SHOULD EXCLUDE DR. KEYES' OPINIONS ABOUT A CAUSAL RELATIONSHIP BETWEEN PRESCRIPTION OPIOIDS AND *SYNTHETIC OPIOID-RELATED HARMS*.

Defendants seek to exclude Dr. Keyes' opinions regarding the alleged relationship between prescription opioids and synthetic-opioid related harms.[15] They are not, as Plaintiffs suggest, revisiting "gateway" issues about whether studies about non-medical use of prescription opioids could be used to show a potential relationship between medical use of prescription opioids and heroin, which were addressed in Track One. *See* ECF No. 3858-2 at 2 n.2; *see also* ECF No. 3797. As discussed in Defendants' Memorandum, and not disputed in Plaintiffs' Opposition, Dr. Keyes' opinions regarding synthetic opioids have never been advanced outside the courtroom, cite no studies, and have not been scientifically tested in any way. And while Plaintiffs dispute that these opinions are based on Dr. Keyes' say-so, they concede that Dr. Keyes relies on "inference[s]" to reach them. These "inferences," however, are not a sound methodology. ECF No. 3858-2 at 12–16; *see Gen. Elec. Co. v. Joiner*, 522 U.S. 136, 146 (1997) (a court should not admit opinions "connected to the existing data only by the *ipse dixit* of the expert"); *see also, e.g.*, *Nelson v. Tenn.*

[15] Synthetic opioids differ from heroin. Dr. Keyes' opinions that Defendants argue should be excluded are about illicit synthetic opioids, like fentanyl, that she recognizes drug dealers have introduced into the illegal drug supply. *See, e.g.*, ECF No. 3858-4 at 39 & 55.

Gas. Pipeline Co., 243 F.3d 244, 253–54 (6th Cir. 2001); *Tamraz v. Lincoln Elec. Co.*, 620 F.3d 665, 669-72 (6th Cir. 2010).[16]

To illustrate the flaw of these "inferences," and Plaintiffs' mischaracterization of Defendants' arguments, it is helpful to examine Dr. Keyes' "*estimate* that approximately 70–80% of fentanyl-involved opioid deaths are attributable to prescription opioid use." ECF No. 3858-4 at 39 (emphasis added). While it is true that Dr. Keyes cites some studies that show that, at certain points in time, approximately 70–80% of individuals who later used heroin misused prescription opioids first (and the percentages have differed over time, and have been lower in other studies), those studies only discuss a sequence of events--which opioid was misused first.[17] Thus, as explained in Defendants' Memorandum, it is highly improper—both speculative and misleading—to state, especially on outdated data, that 70–80% of fentanyl-involved opioid deaths are

[16]*Nelson* and *Tamraz* are discussed in the Reply Memorandum in Further Support of Certain Defendants *Daubert* Motion to Exclude the Opinions Offered by James Rafalski. In footnotes 15 and 16, Plaintiffs cite cases purportedly to support their argument that Dr. Keyes relied on studies and her experience. These cases do not help Plaintiffs. Dr. Keyes does not cite a single study about a causal relationship between synthetic opioid-related harms. One of the cases that Plaintiffs cite in footnote 15 demonstrates the flaws in Plaintiffs' use of these cases. In the section of *In re Heparin Products Liability Litigation*, 803 F. Supp. 2d 712 (N.D. Ohio 2011) that Plaintiffs cite, the expert relied on studies about the specific issue on which she was opining. *Id.* at 736–37 ("Dr. Hoppensteadt explained that this opinion is based on the Adiguzel study conducted at Loyola, which she co-authored, and a review of relevant scientific literature on contaminated heparin and HIT."); *id.* at 737 ("Dr. Hoppensteadt's opinion that OSCS contaminated heparin increases the risk of HIT is supported by her research and the published studies of others."). But in the next section of the opinion, the Court (in a situation analogous to the one here) excluded a separate opinion, because the same expert (a) was theorizing, (b) had done no experiments to confirm her theory, and (c) could not point to any studies published by others that confirmed her theory. The Court went on to state: "Untested hypotheses, even if plausible, are insufficient to satisfy Rule 702. *Id.* at 738 (citation omitted). That Court, as Defendants suggest should occur her, relied on *Tamraz* for the proposition that a "working hypothesis" is not "admissible scientific knowledge." *Id.* The Court also excluded other opinions by the same expert for similar reasons.

[17] Plaintiffs take issue with describing these studies as discussing a "sequence of events," Opp'n 11, but that is literally what they do. For example, the Cicero study looks at what percentages of people misused heroin versus prescription opioids first, and how that has changed over time. It is not a basis to infer causation simply because one opioid is misused before another opioid, especially when, as shown by Cicero, that sequence has flipped over time. ECF No. 3858-2 at 12–13 & n.15. They also argue that Defendants'' statement that "it is quite possible that the percentages overestimate the individuals who misused prescription opioids before heroin" is "conjecture." Opp'n 12. But that statement rests on a solid foundation: Dr. Keyes is drawing the 70–80% figure from outdated data about whether an individual misused prescription opioids or heroin first. *See, e.g.*, ECF No. 3858-29 at 823 ("Beginning in 2010 (2010-2013), these trajectories showed a shift in direction (i.e., heroin use increased as the first opioid of abuse and prescription opioid use decreased), although the data are based on only 3 years of data collection.").

"attributable" to prescription opioid use. Again, Dr. Keyes has not published this "estimate" anywhere;[18] she cites no study that found any such a relationship;[19] and she has done nothing to evaluate whether data (as opposed to her supposition) supports it. ECF No. 3858-2 at 12–16.

With nothing to support Dr. Keyes' synthetic opioid opinions, Plaintiffs invite error by throwing several arguments at the wall. Each should be rejected. First, they say that Dr. Keyes evaluated studies about an association between prescription opioid use and heroin. Opp'n 11–14. Defendants did not ignore those studies; indeed, they noted that some of them are the first step in Dr. Keyes' flawed analysis, and then explained why her "inferences" from those studies to her "estimates" about harms from illicit synthetic opioids are methodologically unsound. ECF No. 3858-2 at 12–16. Second, Plaintiffs argue that Defendants have a "short-sighted focus on the relatively small percentage of prescription opioid users [who go on to use heroin]." Opp'n 13–14. But Defendants never raised this point, and it has nothing to do with their argument. Third, Plaintiffs chastise Defendants for saying Dr. Keyes did not undertake the appropriate analysis, such as considering confounding factors, alternative explanations, or statistical analysis, before "attributing" synthetic opioid-related harms to prescription opioids. Opp'n 15. But that criticism

[18] On page 17 of their Opposition, Plaintiffs cite two studies that they assert that Dr. Keyes has published on the "gateway" effect from prescription opioids to heroin. Neither of the articles they cite addresses that topic and, even if they did, the issue is that she has not published her opinions about synthetic opioid-related harms.

[19] At footnote 23 of their Opposition, Plaintiffs pull a quote from a publication that they say supports Dr. Keyes' testifying to the causal connection between the transition from prescription opioids to heroin and fentanyl use. As an initial matter, the document cited does not examine whether there is a causal relationship between prescription opioids and fentanyl use. Furthermore, the quoted paper cites two studies for the sentence quoted. Neither of those studies describes a causal relationship between prescription opioids and fentanyl or other illicit synthetic opioids. Reply, Exs. 3 & 4.

was correct. The fact that Dr. Keyes cited other studies, such as the Powell study, that considered confounding factors when conducting a different analysis, is irrelevant.[20]

Accordingly, for the reasons explained in Defendants' Memorandum and here, Dr. Keyes' opinions about the purported causal relationship between prescription opioids and synthetic opioid-related harms should be excluded.

III. DR. KEYES' CAUSAL ANALYSIS IS HIGHLY MISLEADING, CONFUSING, AND UNFAIRLY PREJUDICIAL.

In their Memorandum, Defendants explain why statements that prescription opioids are "responsible" for harms from illicit synthetic opioids, that 70–80% of fentanyl-related deaths are "attributable" to prescription opioids, and that "a minimum of 53.4% of [opioid] deaths are indirectly due to prescription opioids," are incorrect. ECF No. 3858-2 at 16–18. Plaintiffs offer no explanation of how such statements are not misleading, confusing, and unfairly prejudicial.[21]

Nor do Plaintiffs dispute that a jury—in a case where causation is a core issue—will be misled and confused by Dr. Keyes' use of the word causation, and words meant to convey causation, like "attributable." *See Daubert v. Merrell Dow Pharms., Inc.*, 509 U.S. 579, 595 (1993) (recognizing expert evidence "can be both powerful and quite misleading because of the difficulty in evaluating it"). Plaintiffs' defense is that they are talking about a different kind of causation,

[20] The Powell study looked at whether Medicare Part D data. Reply, Ex. 5. It drew "on evidence [] that states with higher elderly share have higher Part D enrollment and that enrollment in Part D increased the amount of opioid prescribed to individuals 65 years and older" to "test whether the overall supply of opioids increased disproportionately in high elderly share states." *Id.* at 5. The authors "establish[ed] that the medical distribution of opioids (from producers) is higher to states with a higher elderly share after implementation of Medicare Part D[.]" *Id.* The authors then examined "whether this differential increase in opioid supply led to disparate growth in opioid abuse rates among the under-65 population as measured by overdose deaths and using a complementary measure of opioid substance abuse treatment admissions." *Id.* The authors note that "our evidence suggests that 73% of the dramatic growth in opioid-related overdose deaths can be attributable to spillovers resulting from increased medical access." *Id.* at 6. The study has nothing to do with synthetic-opioid related harms.

[21] To be clear, Dr. Keyes' estimate will never be supported by evidence. Plaintiffs are not going to show that 70–80% of fentanyl-related deaths are attributable to prescription opioids, let alone whether prescription opioids distributed or dispensed by a Defendant caused such harm. To do so, they would have to trace prescription opioids to harm suffered by an individual and delve into the individual circumstances of people who unfortunately overdose on fentanyl. Plaintiffs have stated that they will not prove their case in this manner.

"factual causation," as opposed to legal causation. Opp'n 18. In their telling, Dr. Keyes will opine about "the correlation between the rise in prescription opioids use and increased heroin and fentanyl-related harms." *Id.* That is false, as shown by the statements quoted above, and as discussed in Defendants' Memorandum, *see* ECF No. 3858-2 at 16–18. Indeed, Plaintiffs admit as much when they argue later in their Opposition that Dr. Keyes' testimony "should not be foreclosed merely because she may use particular words *attributing a causal relationship*." Opp'n 19 (emphasis added). Dr. Keyes should be precluded from offering such testimony.

At the very least, this Court should provide a limiting instruction, following Dr. Keyes' testimony, that explains, consistent with Plaintiffs' position, that Dr. Keyes' use of words like "responsible," "attributable," and "causation" do not describe legal causation, and that the Court alone will instruct on legal causation.[22] Such an instruction would be appropriate in any case, but this Court vigilantly guarding against such confusing and misleading testimony is absolutely necessary in a case that imposes strict time limits on Defendants that will prevent lengthy examinations of witnesses.

CONCLUSION

For the reasons explained in Defendants' Memorandum and above, this Court should grant Defendants' Motion to Exclude Certain Opinions of Dr. Katherine Keyes.

[22] Defendants reserve the right to propose an appropriate instruction. For example, the instruction should make clear that Dr. Keyes is not opining that all heroin use (or opioid-related harms) resulted from prescription opioid use. Indeed, Dr. Keyes' casual attribution, even as to heroin, means only that prescription opioids use is a "risk factor" for heroin use, and that some individuals in the general population use heroin as a result of using prescription opioids. ECF No. 3858-4 at 11 ("I will apply the [] 'risk factor' framework to my assessment of the causes of the opioid crisis, considering factors to be causes of opioid use disorder, overdose, and related harms if *some cases* would not have occurred in the absence of prescription opioid use. This framework does not preclude or ignore that addiction and related harms *are multi-factorial in their etiology*, but rather asks whether there are *cases* for which the outcome would not have occurred without the presence of prescription opioid use.") (emphasis added). To determine whether a specific individual used heroin as a result of using prescription opioids, one would need to examine that individual's drug use and other factors. *See, e.g.*, Federal Judicial Center, Reference Manual for Scientific Evidence at 608 (3d ed. 2011) ("Epidemiology is concerned with the incidence of disease in populations, and epidemiologic studies do not address the question of the cause of an individual's disease. This question, often referred to as specific causation, is beyond the domain of the science of epidemiology.") (footnote omitted).

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CERTIFICATE OF SERVICE

I, the undersigned, hereby certify that the foregoing document was served via email to all counsel of record, the Court, and Special Master Cohen on August 27, 2021.

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